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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/944,929	08/31/2001	Kevin P. Baker	P2548P1C21	2450

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EXAMINER
VOGEL, NANCY S

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
09/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/944,929	BAKER ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 27-41 are pending in the case.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/19/07 has been entered.

The rejection of claims 27-41 made under 35 U.S.C. §101 for a lack of utility is being withdrawn. In a review of the prior art in an application related to the instant application, art was discovered which was persuasive in establishing that the MLR assay is an art accepted assay for identifying immune suppressive molecules and the assay is generally predictive of their *in-vivo* effectiveness. (See column 12, lines 36-41 of U.S. Pat. No. 5,817,306).

The following is considered a new rejection since new arguments for support are presented:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims 27-41 are drawn to a nucleic acid that encodes antibody the polypeptide of SEQ ID NO:83, said polypeptide designated as PRO 361. The specification at page 141 states "compounds which inhibit proliferation of lymphocytes are useful

therapeutically where suppression of an immune response is beneficial".. However, the ability of the protein of SEQ ID NO:83 to inhibit lymphocyte proliferation in the MLR assay does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function for a therapeutic suppression of the immune system. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not enabled by the disclosure of the instant specification. The

only use contemplated for the claimed invention is a therapeutic suppression of the immune system. Kahan clearly states that no *in-vitro* immune assay predicts or correlates with *in-vivo* immunosuppressive efficacy; there is no surrogate immune

parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol. 4: 553-560, 1992, see entire document, particularly page 558, column 2). Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as etermined by MLC, but this result *in-vitro* does not result in a measurable response #7-*vivo* (i.e. failure to accelerate allograft rejection), (see page 1459). Campo et al. (Biological Trace Element Res. 79: 15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation in vitro nor produce immunosuppressive effects in-vivo. Therefore, while the art recognizes the MLR assay is accepted for screening for immunosuppressive molecules in-vitro, which is art recognized for being generally predictive of their in vivo effectiveness, this biological activity does not correlate to use of the claimed protein in a therapeutically effective manner, as the asserted use of the claimed invention proposes. The MLR assay is an accepted in-vitro model for screening immunosuppressive agents for use in the prevention of graft-versus-host disease and graft rejection. However, the assay must be evaluated as it pertains to the asserted use of the claimed invention, which is for therapeutic enhancement of the immune response of an individual. If the claimed invention is to be used for therapeutic enhancement of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted utility of the claimed invention? The results of the MLR assay in the instant specification are merely preliminary, and much more experimentation is necessary for one of ordinary skill in the art to use the claimed invention in the manner disclosed. This

experimentation would be considered undue, because until it is performed, the skilled artisan cannot use the claimed invention in the manner disclosed. Because the claimed invention is not enabled and does not meet the its of 112 first paragraph for the reasons provided above, the instant requirement application is not afforded benefit of the earlier filed applications.

Furthermore, the relevant art recognizes that compounds that show promising results in *in-vitro* immune assays do not always lead to *in-vivo* safety and/or efficacy outcome. For example, volunteers receiving the drug TGN1412 aimed at treating leukemia and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis, became seriously ill and were hospitalized, (see Vogel, Science Vol 311, pages 1688-1689, March 2006). Extensive preclinical tests of this drug showed no sign of any risk, therefore, the volunteers' reaction was not foreseeable, (page 1689). Thus, treatments involving the suppression or stimulation of immune cells have to be studied carefully, because immune cells are involved in so many disparate processes, that over stimulation or over suppression can lead to undesired detrimental effects. The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant case, the only asserted use for the

claimed invention is therapeutic use, however, there is no guidance in the specification as to the specific conditions or disorders that the claimed invention is useful for. Therefore, due to the lack of guidance in the specification, the complex nature of the invention coupled with the state of the prior art, which establishes that the safety and efficacy of pharmaceuticals involving immune suppressors cannot be predicted from *in-vitro* studies, the claimed invention is rendered nonenabling.

Furthermore, even if the instant specification provides an enabling disclosure for the polypeptide of SEQ ID NO:83, and therefore the DNA encoding the polypeptide, absent factual evidence, a DNA which hybridizes under stringent conditions to SEQ ID NO:82, which encodes said polypeptide SEQ ID NO:83, is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as
that of such a similar known biomolecule. Accordingly, a nucleic acid which hybridizes under stringent conditions to the nucleic acid encoding SEQ ID NO:83, or SEQ ID NO:82, would not
be found to be enabled. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement.

Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research (see Wells, 1990, Biochemistry 29:8509-8517).

Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the sequence which are tolerant to change (e.g. such as by substitutions or deletions), and the nature and extent of changes that can be made in these positions. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure and still maintain sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. Therefore, an isolated nucleic acid that hybridizes under stringent conditions to a nucleic acid encoding SEQ ID NO:83, is non-enabling.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NANCY VOGEL
PRIMARY EXAMINER

NTV
9/15/07